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09/666,870	09/20/2000	Andrew D. Ellington	119927-1030	8382

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EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-49 and 54-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-49 and 54-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

4) ☐ Interview Summary (PTO-413)

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/11/04 has been entered. Claims 47, 54, 59 and 62 were amended. No claims were added or canceled. Therefore, claims 47-49 and 54-66 are currently pending and active in the instant application. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Maintained Rejections and/or Objections

Claims Rejections - 35 U.S.C. 102

2. Claims 47, 49, 54-59 and 61-66 are rejected under 35 U.S.C. 102(a) as being anticipated by Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" Nature Structural Biology **November 1999**, 6 (11), 992-4).

For ***claims 47, 59 and 66***, Marshall et al discloses "aptazyme chips" wherein different ribozyme ligases are immobilized on beads in wells to monitor the presence and concentrations of different metabolites or proteins (see Marshall et al, entire document,

especially figure 3; see also page 994, last paragraph), which anticipates claims 47, 59 and 66. For example, Marshall et al discloses aptazyme chips for "monitor[ing] the presence and concentrations of different metabolites or proteins" wherein a "ribozyme ligase", which anticipates the preamble of claim 47 because an "aptazyme reaction" is being "detected" when the ribozyme ligase covalently bonds to a reporter in the presence of cognate effectors. Marshall et al also discloses "aptazymes" on a solid support, which reads on lines 2-5 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... are shown immobilized on beads in wells ... [o]ne advantage of this scheme is that covalent immobilization of reporters ... should allow extremely stringent wash steps to be employed"). Marshall et al also discloses "at least one analyte" and "providing substrate tagged to be detectable" in lines 7-8 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... immobilized on beads in wells and mixtures of <u>analytes</u> and fluorescently <u>tagged substrates</u> have been added to each well"). Marshall et al also discloses the immobilization of a substrate to the aptazyme upon activation of the aptazyme with an analyte wherein a signal is produced after washing unbound substrate off the substrate (see Marshall et al, figure 3, "after reaction and washing, the presence and amounts of co-immobilized fluorescent tags are indicative of he amounts of ligands that were present during the reaction"). Please also note that Marshall et al discloses applicants preferred embodiment (compare Marshall et al, figure 3 and page 994, last paragraph to applicant's specification, pages 60-61, especially page 60, line 19 which references the Marshall et al paper).

For **claims 49 and 61**, Marshall et al discloses the use of "amplification" for increasing the amount of aptamer or aptazyme with the desired characteristics and thus increase the signal produced (see Marshall et al, figure 1) (see also Marshall, page 994 last paragraph, "Interestingly, aptazyme ligases have the unique property of being able to transduce effectors into templates that can be amplified, affording an additional boost in signal prior to detection"), which anticipates claim 49.

For ***claims 54 and 62***, Marshall et al discloses fluorescently tagged substrates (see Marshall et al, page 993, figure 3).

For ***claims 55-56 and 63-64***, Marshall et al discloses beads in wells on a multiwell plate (see Marshall et al, page 993, figure 3).

For ***claim 57***, Marshall et al discloses different aptazymes immobilized in different wells (see Marshall et al, page 993, figure 3).

For ***claims 58 and 65***, Marshall et al discloses metabolites and proteins (see Marshall et al, page 993, figure 3).

3. Claims 47, 49, 54, 58, 61-62 and 65-66 are rejected under 35 U.S.C. 102(a) as being anticipated by Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. "In vitro selection of nucleic acids for diagnostic applications" Reviews in Molecular *Biotechnology* **March 2000**, *74*, 15-25).

For ***claims 47, 59 and 66***, Hesselberth et al discloses methods for the "high-throughput construction of chips to sense proteomes and metabolomes" (see Hesselberth

et al, entire document, pages 23-24; section 5), which anticipates claims 47, 59 and 66. For example, Hesselberth et al discloses that "aptazymes" can be "covalently immobilize[d] ... in discrete sectors of arrays" like "chip[s]" (see Hesselberth et al, page 24, last paragraph, "For example, a host of signaling aptamers could be synthesized with terminal amines, immobilized on glass, and an analyte mixture could be applied to the glass surface"). Hesselberth et al also discloses method steps for using the immobilized aptazymes to detect individual analytes by their ability to "pull down" labeled substrates that can then be detected after washing away unbound substrate (see Hesselberth et al, page 24, last paragraph, "The presence of quantities of individual analytes could then be determined by monitoring the changes in fluorescence intensity in individual sectors of the chip. Similarly, aptazymes could be immobilized and analytes and oligonucleotide tags introduced together. Since the pairing between the aptazymes and the oligonucleotide tags can be altered at will, analytes could activate specific aptamers in specific sectors to pull down specific tags. In this way, analyte detection might not only be spatially but also spectrally resolved. Moreover because the tags are covalently immobilized to the aptazyme, which in turn covalently immobilized to the chip surface, aptazyme chips can be stringently washed to reduce non-specific binding and background").

For ***claims 49 and 61***, Hesselberth et al discloses the ribozymes with appended tags can be "preferentially amplified" (see Hesselberth et al, entire document, especially page 16, paragraph 1), which anticipates claim 49.

For ***claims 54 and 62***, Hesselberth et al discloses fluorescent substrates (see Hesselberth et al, page 24, column 1, last paragraph).

For ***claims 58 and 65***, Hesselberth et al discloses proteins (see Hesselberth et al, page 19, column 1, paragraph 1; see also page 23, column 2, paragraph 2).

Response

4. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection(s) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues that the references cited above do not constitute prior art because they represent the work of the presently claimed inventors as set forth in the 2/11/2004 Affidavit (131 or 132).

This is not found persuasive for the following reasons:

The Examiner contends that the Declaration is defective because the inventorship is not consistent with Applicants' oath i.e., Kristin Thompson (formerly Kristin Marshall) is not listed as a co-inventor (see below).

Accordingly, the 35 U.S.C. 102 rejection(s) cited above are hereby maintained.

Claims Rejections – 35 U.S.C. 102/103

5. Claims 47-49 and 54-66 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in

Ellington, A. D. "Training ribozymes to switch" Nature Structural Biology **November 1999**, 6 (11), 992-4).

For ***claims 47, 59 and 66***, Marshall et al discloses "aptazyme chips" wherein different ribozyme ligases are immobilized on beads in wells to monitor the presence and concentrations of different metabolites or proteins (see Marshall et al, entire document, especially figure 3; see also page 994, last paragraph), which anticipates claims 47, 59 and 66. For example, Marshall et al discloses aptazyme chips for "monitor[ing] the presence and concentrations of different metabolites or proteins" wherein a "ribozyme ligase", which anticipates the preamble of claim 47 because an "aptazyme reaction" is being "detected" when the ribozyme ligase covalently bonds to a reporter in the presence of cognate effectors. Marshall et al also discloses "aptazymes" on a solid support i.e., they are disclosing "apatazyme chips", which reads on lines 2-5 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... are shown immobilized on beads in wells ... [o]ne advantage of this scheme is that covalent immobilization of reporters ... should allow extremely stringent wash steps to be employed"). Marshall et al also discloses "at least one analyte" and "providing substrate tagged to be detectable" in lines 7-8 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... immobilized on beads in wells and mixtures of <u>analytes</u> and fluorescently <u>tagged substrates</u> have been added to each well"). Marshall et al also discloses the immobilization of a substrate to the aptazyme upon activation of the aptazyme with an analyte wherein a signal is produced after washing unbound substrate off the substrate (see Marshall et al, figure 3, "after reaction and

washing, the presence and amounts of co-immobilized fluorescent tags are indicative of he amounts of ligands that were present during the reaction").

For **claims 48 and 60**, although Marshall et al does not specifically mention the use of "automation" with disclosed methods for using "aptazyme chips", automation would be would be immediately envisaged (e.g., anticipated) or in the alternative prima facie obvious to one of ordinary skill in the art because "chip" are made for automation i.e., they are used and designed for high throughput screening. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

For **claims 49 and 61**, Marshall et al discloses the use of "amplification" for increasing the amount of aptamer or aptazyme with the desired characteristics and thus increase the signal produced (see Marshall et al, figure 1) (see also Marshall, page 994 last paragraph, "Interestingly, aptazyme ligases have the unique property of being able to transduce effectors into templates that can be amplified, affording an additional boost in signal prior to detection"), which anticipates claim 49.

For ***claims 54 and 62***, Marshall et al discloses fluorescently tagged substrates (see Marshall et al, page 993, figure 3).

For ***claims 55-56 and 63-64***, Marshall et al discloses beads in wells on a multiwell plate (see Marshall et al, page 993, figure 3).

For ***claim 57***, Marshall et al discloses different aptazymes immobilized in different wells (see Marshall et al, page 993, figure 3).

For ***claims 58 and 65***, Marshall et al discloses metabolites and proteins (see Marshall et al, page 993, figure 3).

6. Claims 47-49, 56, 58-62 and 65-66 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. "In vitro selection of nucleic acids for diagnostic applications" Reviews in Molecular Biotechnology March 2000, 74, 15-25).

For ***claims 47, 59 and 66***, Hesselberth et al discloses methods for the "high-throughput construction of chips to sense proteomes and metabolomes" (see Hesselberth et al, entire document, pages 23-24; section 5), which anticipates claim 47. For example, Hesselberth et al discloses that "aptazymes" can be "covalently immobilize[d] ... in discrete sectors of arrays" like "chip[s]" (see Hesselberth et al, page 24, last paragraph, "For example, a host of signaling aptamers could be synthesized with terminal amines, immobilized on glass, and an analyte mixture could be applied to the glass surface"). Hesselberth et al also discloses method steps for using the immobilized aptazymes to detect individual analytes by their ability to "pull down" labeled substrates that can then be detected after washing away unbound substrate (see Hesselberth et al, page 24, last paragraph, "The presence of quantities of individual analytes could then be determined by monitoring the changes in fluorescence intensity in individual sectors of the chip. Similarly, aptazymes could be immobilized and analytes and oligonucleotide tags introduced together. Since the pairing between the aptazymes and the oligonucleotide tags can be altered at will, analytes could activate specific aptamers in specific sectors to pull down specific tags. In this way, analyte detection might not only be spatially but

also spectrally resolved. Moreover because the tags are covalently immobilized to the aptazyme, which in turn covalently immobilized to the chip surface, aptazyme chips can be stringently washed to reduce non-specific binding and background").

For ***claims 48 and 60***, although Hesselberth et al does not specifically mention the use of "automation" with disclosed methods for using the "chips", automation would be would be immediately envisaged (e.g., anticipated) or in the alternative prima facie obvious to one of ordinary skill in the art because "chip" are made for automation i.e., they are used and designed for high throughput screening. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

For ***claims 49 and 61***, Hesselberth et al discloses the ribozymes with appended tags can be "preferentially amplified" (see Hesselberth et al, entire document, especially page 16, paragraph 1), which anticipates claim 49.

For ***claims 54 and 62***, Hesselberth et al discloses fluorescent substrates (see Hesselberth et al, page 24, column 1, last paragraph).

For ***claims 58 and 65***, Hesselberth et al discloses proteins (see Hesselberth et al, page 19, column 1, paragraph 1; see also page 23, column 2, paragraph 2).

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 102/103 rejection(s) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims

Applicant argues that the references cited above do not constitute prior art because they represent the work of the presently claimed inventors as set forth in the 2/11/2004 Affidavit (131 or 132).

This is not found persuasive for the following reasons:

The Examiner contends that the Declaration is defective because the inventorship is not consistent with Applicants' oath i.e., Kristin Thompson (formerly Kristin Marshall) is not listed as a co-inventor (see below).

Accordingly, the 35 U.S.C. 102/103 rejection(s) cited above are hereby maintained.

Claim Rejections - 35 USC § 103

8. Claims 47-49, 54-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" Nature Structural Biology **November 1999**, 6 (11), 992-4) and Cox et al (Cox, J. C.; Rudolph, P.; Ellington, A. D. "Automated RNA Selection" *Biotechnol. Prog.* **1998**, 14, 845-850).

For **claims 47, 49, 54-59 and 61-66**, Marshall et al teaches all the limitations stated in the 35 U.S.C. 102(a) rejection above (incorporated in its entirety herein by reference), which anticipates claims 47, 49, 54-59, 61-66 and, consequently, also renders obvious claims 47, 49, 54-59, 61-66.

For ***claims 48 and 60***, the prior art teachings of Marshall et al differs from the claimed invention by not specifically reciting the use of a "automation" for the method of detecting an aptazyme reaction. Marshall et al is deficient in that it only teaches the use

of "chips", which only implies that automation would be used since chips are designed for large scale automation (see Marshall et al, page 993, figure 3).

However, Cox teaches that in vitro selection can be "automated" (see entire document, especially figure 1).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method of Marshall et al with the "automation" equipment as taught by Cox et al because Cox et al teaches that their automation procedures can be used with aptamers in procedures that involve in vitro selection as required by the method steps Marshall et al. Furthermore, one of ordinary skill in the art would have been motivated to use a "automation" because Cox explicitly states that "[a]utomated selection can now be used to generate nucleic acid aptamers in days rather than weeks or months" i.e. one of skill in the art would have immediately recognized the time savings that could be obtained through automation and the possibility of increased throughput (see Cox et al, entire document, especially abstract).

9. Claims 47, 49, 54, 58, 61-62 and 65-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. "In vitro selection of nucleic acids for diagnostic applications" Reviews in Molecular Biotechnology March 2000, 74, 15-25) and Cox et al (Cox, J. C.; Rudolph, P.; Ellington, A. D. "Automated RNA Selection" Biotechnol. Prog. **1998**, 14, 845-850).

For **claims 47, 49, 54, 58, 61-62 and 65-66**, Hesselberth et al teaches all the limitations stated in the 35 U.S.C. 102(a) rejection above (incorporated in its entirety herein by reference), which anticipates claims 47, 49, 54, 58, 61-62, 65-66 and, consequently, also renders obvious claims 47, 49, 54, 61-62, 65-66.

For ***claims 48 and 60***, the prior art teachings of Hesselberth et al differs from the claimed invention by not specifically reciting the use of a "automation" for the method of detecting an aptazyme reaction. Hesselberth et al is deficient in that it only teaches the use of "chips", which only implies that automation would be used since chips are designed for large scale automation (see Hesselberth et al, page 24, last paragraph; see also abstract).

However, Cox teaches that in vitro selection can be "automated" (see entire document, especially figure 1).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method of Hesselberth et al with the "automation" equipment as taught by Cox et al because Cox et al teaches that their automation procedures can be used with aptamers in procedures that involve *in vitro* selection as required by the method steps Hesselberth et al. Furthermore, one of ordinary skill in the art would have been motivated to use a "automation" because Cox explicitly states that "[a]utomated selection can now be used to generate nucleic acid aptamers in days rather than weeks or months" i.e. one of skill in the art would have immediately recognized the time savings that could be obtained through automation and the possibility of increased throughput (see Cox et al, entire document, especially abstract).

Response

10. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection(s) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues that the references cited above do not constitute prior art because they represent the work of the presently claimed inventors as set forth in the 2/11/2004 Affidavit (131 or 132).

This is not found persuasive for the following reasons:

The Examiner contends that the Declaration is defective because the inventorship is not consistent with Applicants' oath i.e., Kristin Thompson (formerly Kristin Marshall) is not listed as a co-inventor (see below).

Accordingly, the 35 U.S.C. 103(a) rejection cited above is hereby maintained.

New Rejections and/or objections

Oath/Declaration

11. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application-by-application number and filing date is required. See MPEP §§ 602.01 and 602.02.

In view of the Affidavits (131 or 132) submitted on February 11, 2004 (see especially page 1, paragraph 1), it is clear that the oath or declaration is defective because Kristin Thompson (formerly Kristin Marshall) is not listed as a co-inventor i.e., the full name of

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 47-49 and 54, 58-63, 65-66 are rejected under 35 U.S.C. 102(a) as being anticipated by Breaker et al. (WO 00/26226) (Date of Patent is **May 11, 2000**).

For ***claims 47, 59 and 66***, Breaker et al. (see entire document) disclose methods for making and using "aptazyme chips", which anticipates claims 47 and 59. For example, Breaker et al. disclose providing a solid support having a heterogeneous mixture of aptazyme constructs covalently immobilized thereon (e.g., see figure 17 wherein aptazyme constructs cGMP, ATP, FMN, theo and cAMP are shown immobilized on positions A1, A2, A3, A4 and B1, respectively; see also column 4, lines 17; see especially page 21, line 21). Breaker et al. also disclose at least one analyte (e.g., see figure 16 wherein the DNA is exposed to a sample of interest e.g., ATP). Breaker et al. also disclose providing a nucleic acid substrate tagged to be detectable exposing the nucleic acid substrate and at least one analyte to the immobilized aptazymes, whereby activation of the aptazyme reaction by the analyte produces a signal when the nucleic

acid substrate is bound to the immobilized aptazymes, washing unbound substrate off the solid support and detecting the signal from the bound nucleic acid substrate (e.g., see black spots in figure 16; see also page 17, lines 10-19; see also Examples).

For ***claim 48 and 60***, Breaker et al. disclose automation (e.g., see page 21, line 19 wherein "automation" is disclosed)

For ***claims 49 and 61***, Breaker et al. disclose signal amplification (e.g., see page 24, line 8 wherein "PCR amplification" is disclosed; see also page 10, lines 17-19 wherein signal amplification is conducted via enzymatic cleavage of substrate).

For ***claims 54 and 62***, Breaker et al. disclose, for example, fluorescent tags (e.g., see page 17, line 16).

For ***claims 55 and 63***, Breaker et al. disclose a multiwell plate (e.g., see page 36, line 29 wherein a microtiter plate is disclose; see also figure 16).

For ***claim 58 and 65***, Breaker et al. disclose cGMP, ATP, FMN, theo, cAMP (e.g., see figure 16), which anticipate metabolites. Breaker et al. also disclose proteins (e.g., see page 16, last paragraphs).

13. Claims 66 is rejected under 35 U.S.C. 102(b) as being anticipated by Asher et al. (WO 98/08974) (Date of Publication is March 5, 1998).

For ***claim 66***, Asher et al. disclose (see entire document) catalytic nucleic acids and their diagnostic use (see Asher et al, abstract), which anticipates claim 66. For example, Asher et al. disclose providing an array having one or more aptazyme

constructs disposed thereon at discrete locations by immobilization of said aptazyme constructs on a solid support (e.g., see figure 1 step 3 showing the immobilization processes using streptavidin/avidin as the linker; see also page 4, lines 18-22, "The biotin, is then allowed to react with avidin which is present on a solid support, such as Stepravidin beads (SA), so that each molecule of the random array becomes immobilized onto a solid support"). Please note that the aptazyme constructs in this scenario comprise a random sequence (R) that cleave the substrate (S) in "cis" (e.g., see page 24, Example 1, lines 9-15; see also figure 1, step 1, see also figure 1, step 4(b)(i) and 4(b)(ii); see also page 14, lines 21-29). In addition, Asher et al. disclose contacting said aptazyme constructs with a substrate tagged with a detectable label (e.g., see figure 1, step 1 wherein the substrate is represented by the "S" i.e., the aptazyme is cis-acting; see also figure 1, step 6 wherein a PCR amplified tag is shown; see also page 16, last paragraph; see also page 8, lines 10-15, "For example, the catalytic complex may cleave, from an immobilized nucleic acid substrate, a small fragment bearing a detectable label. Then, detection of a free label in the reaction medium is indicative of the activity of the catalytic complex, which is in turn an indication of the presence of the assayed agent in the medium"). Asher et al. also disclose aptazyme constructs that bind to said tagged substrates in the presence of an analyte, but do not bind to said tagged substrates in the absence of said analyte (e.g., see figure 1, step 4(a) showing "Pro" i.e., a protein analyze; see also abstract, "The present invention concerns nucleic acid molecules [aptazymes] ... which have no catalytic activity in the absence of a specific co-factor [i.e., the "Pro"], and feature catalytic activity only in the presence of a specific co-factor"; see also Examples

which employ multiple rounds of positive and negative screening steps to obtain this goal). Finally, Asher et al. also disclose contacting said aptazyme constructs and substrate within a sample suspected of containing said analyte under conditions which allow for substrate binding, washing away unbound substrate and detecting the bound substrate, thereby determining the presence of the analyte (e.g., see figure 1, steps 4-5, especially step 4 showing unbound substrate being "washed" off the solid support; see also claims 1, 9 and 15; see also page 31, "Negative Selection" step).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 47-49 and 54-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asher et al (WO 98/08974) (Date of Publication is **March 5, 1998**) and Breaker (WO 98/27104) (Date of Publication is **June 25, 1998**).

For ***claims 47, 59 and 66***, Asher et al. disclose (see entire document) catalytic nucleic acids and their diagnostic use (see Asher et al, abstract), which reads on claims 47, 59 and 66. For example, Asher et al. disclose providing an array having one or more aptazyme constructs disposed thereon at discrete locations by immobilization of said aptazyme constructs on a solid support (e.g., see figure 1 step 3 showing the immobilization processes using streptavidin/avidin as the linker; see also page 4, lines 18-22, "The biotin, is then allowed to react with avidin which is present on a solid support, such as Streptavidin beads (SA), so that each molecule of the random array becomes immobilized onto a solid support"). Please note that the aptazyme constructs in this scenario comprise a random sequence (R) that cleave the substrate (S) in "cis" (e.g., see page 24, Example 1, lines 9-15; see also figure 1, step 1, see also figure 1, step 4(b)(i) and 4(b)(ii); see also page 14, lines 21-29). In addition, Asher et al. disclose contacting said aptazyme constructs with a substrate tagged with a detectable label (e.g., see figure 1, step 1 wherein the substrate is represented by the "S" i.e., the aptazyme is cis-acting; see also figure 1, step 6 wherein a PCR amplified tag is shown; see also page 16, last paragraph; see also page 8, lines 10-15, "For example, the catalytic complex may cleave, from an immobilized nucleic acid substrate, a small fragment bearing a <u>detectable label</u>. Then, detection of a free label in the reaction medium is indicative of the activity of the

catalytic complex, which is in turn an indication of the presence of the assayed agent in the medium"). Asher et al. also disclose aptazyme constructs that bind to said tagged substrates in the presence of an analyte, but do not bind to said tagged substrates in the absence of said analyte (e.g., see figure 1, step 4(a) showing "Pro" i.e., a protein analyze; see also abstract, "The present invention concerns nucleic acid molecules [aptazymes] ... which have no catalytic activity in the absence of a specific co-factor [i.e., the "Pro"], and feature catalytic activity only in the presence of a specific co-factor"; see also Examples which employ multiple rounds of positive and negative screening steps to obtain this goal). Finally, Asher et al. also disclose contacting said aptazyme constructs and substrate within a sample suspected of containing said analyte under conditions which allow for substrate binding, washing away unbound substrate and detecting the bound substrate, thereby determining the presence of the analyte (e.g., see figure 1, steps 4-5, especially step 4 showing unbound substrate being "washed" off the solid support; see also claims 1, 9 and 15; see also page 31, "Negative Selection" step).

For ***claims 49 and 61***, Asher et al disclose amplifying the signal by various means including self amplifying ribozyme cascade reactions and PCR (e.g., see page 9, line 8 wherein a self amplifying ribozyme cascade reaction is reporter; see also page 16, last paragraph).

For ***claims 54 and 62***, Asher et al disclose fluorescently labeled RNA constructs (e.g., see figure 19).

For ***claims 55 and 63***, Asher et al disclose Streptavidin beads (e.g., see page 24, lines 20-21).

For ***claim 58 and 65***, Asher et al disclose, for example, proteins (e.g., see figure 1, step 4(b) wherein "Pro" represents a protein).

The prior art teachings of Asher et al differ from the claimed invention as follows:

For ***claim 47***, Asher et al are deficient in that they do not specifically recite the use of "covalent" immobilization. Asher et al. only disclose the use of streptavidin/avidin as an example (e.g., see figure 1).

For ***claim 48***, Asher et al are deficient in that they do not disclose automation.

For ***claim 56 and 57***, Asher et al are deficient in that they do not disclose a bead in the well of a multiwell plate.

However, Breaker teaches the following limitations that are deficient in Asher et al:

For ***claim 47***, Breaker (see entire document) teaches the use of covalent bonding of the aptazymes to the solid support (e.g., see page 18, lines 6-11, "A variety of different chromatographic resins and coupling methods can be employed to immobilize DNA enzymes. For example, a simple non-covalent method that takes advantage of the strong binding affinity of streptavidin for biotin to carryout a model experiment is illustrated in Figure 3. In other embodiments, DNA enzymes can be coupled to the column supports via covalent links to the matrix, thereby creating a longer-lived catalytic support").

For ***claims 48 and 60***, Breaker discloses automation (e.g., see page 17, line 21).

For ***claims 56 and 57***, Breaker teaches biosensors on a solid-support which are commonly performed on multiwell plates (e.g., see pages 1-2). Furthermore, the beads in the wells would have to contain different constructs in order for the "biosensor" to work

e.g., if they had the same construct immobilized in every well it wouldn't function as a biosensor.

For ***claim 58 and 65***, Breaker et al also disclose metabolites (e.g., see page 4, line 26).

It would have been obvious to one skilled in the art at the time the invention was made to make the immobilized array of aptazymes as taught by Asher et al with covalent attachment of the aptazymes to the solid-support as taught by Breaker instead of by Streptavidin/Avid immobilization as taught by Asher et al because Breaker explicitly states that aptazymes can be immobilized in this fashion and for this purpose (e.g., see page 18, lines 6-11, "A variety of different chromatographic resins and coupling methods can be employed to immobilize DNA enzymes. For example, a simple non-covalent method that takes advantage of the strong binding affinity of streptavidin for biotin to carryout a model experiment is illustrated in Figure 3. In other embodiments, DNA enzymes can be coupled to the column supports via <u>covalent links</u> to the matrix, thereby creating a <u>longer-lived catalytic support</u>"). A person would have been motivated to use toe covalent links taught by Breaker et al because the reference explicitly states that they provide for "longer-lived catalytic support" i.e., they are more stable than the streptavidin/avidin complexes. Finally, one of ordinary skill in the art would have reasonably expected to be successful because Breaker teaches a "wide variety" of coupling methods exist for immobilizing aptazymes including streptavidin/avidin and covalent modification and that all of the methods can be used successfully i.e., these procedures are well known in the art to be successful (see Breaker,).

Furthermore, a person of skill in the art would have also been motivated to use the allosterically controlled "DNA" Enzymes disclosed by Breaker in place of the "RNA" Enzymes disclosed by Asher et al. because Breaker explicitly states that "DNA" enzymes are better than "RNA" enzymes because of their increased stability (e.g., see page 18, paragraph 1, "The function of catalytic DNAs to create enzyme coated surfaces that can be used in various catalytic processes is described herein and illustrated in Figure 4. Due to the high stability of the DNA phosphodiester bond, such surfaces are expected to remain active for much longer than similar surfaces that are be coated with protein- or RNA-based enzymes"). Furthermore, a person of skill in the art would have reasonably expected to be successful because both references state that these nucleic acids (both RNA/DNA) can be used for biological assays.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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